form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Myers (1995) Molecular Biology and Biotechnology: A Comprehensive Desk Reference, VCH Publishers, New York, (see especially Figure 4, page 833) and in Haseloff and Gerlach (1988) Nature, 334, 585-591, each of which is incorporated herein by reference in its entirety.

85. Preferably the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA encoding the enzyme involved in glucosylceramide synthesis, i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

86. The ribozymes of the present invention also include RNA endoribonucleases (hereinafter "Cech-type ribozymes") such as the one that occurs naturally in Tetrahymena thermophila (known as the IVS, or L-19 IVS RNA) and that has been extensively described by Thomas Cech and collaborators (Zaug, et al. (1984) Science, 224, 574-578; Zaug and Cech (1986) Science, 231, 470-475; Zaug, et al. (1986) Nature, 324, 429-433; published International patent application No. WO 88/04300 by University Patents Inc.; Been and Cech (1986) Cell, 47, 207-216). The Cech-type ribozymes have an eight base pair active site which hybridizes to a target RNA sequence whereafter cleavage of the target RNA takes place. The invention encompasses those Cech-type ribozymes which target eight base-pair active site sequences that are present in the gene encoding the enzyme involved in glucosylceramide synthesis.

87. As in the antisense approach, the ribozymes can be composed of modified oligonucleotides (*e.g.*, for improved stability, targeting, etc.) and should be delivered to cells that express the enzyme involved in glucosylceramide synthesis *in vivo*. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous mRNA encoding the enzyme involved in glucosylceramide synthesis and inhibit translation. Because ribozymes, unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficacy.

88. Endogenous expression of an enzyme involved in glucosylceramide synthesis can also be reduced by inactivating or "knocking out" the gene encoding an enzyme involved in glucosylceramide synthesis, or the promoter of such a gene, using targeted homologous recombination (*e.g.*, see Smithies et al. 1985) Nature 317:230-234; Thomas and Capecchi (1987) Cell 51:503-512; Thompson et al. (1989) Cell 5:313-321; and Zijlstra et al. (1989) Nature 342:435-438, each of which is incorporated by reference herein in its entirety). For example, a mutant gene encoding a non-functional an enzyme involved in glucosylceramide synthesis (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous gene (either the coding regions or regulatory regions of the gene encoding an enzyme involved in glucosylceramide synthesis) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express the target gene *in vivo*. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the target gene. Such approaches are particularly suited in the agricultural field where modifications to ES (embryonic stem) cells can be used to generate animal offspring with an inactive target gene. However, this approach can be adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors.

89. Alternatively, the endogenous expression of a gene encoding an enzyme involved in glucosylceramide synthesis can be reduced by targeting deoxyribonucleotide sequences complementary to the regulatory region of the gene (i.e., the gene promoter and/or enhancers) to form triple helical structures that prevent transcription of the gene encoding an enzyme involved in glucosylceramide synthesis in target cells in the body. (See generally, Helene (1991) Anticancer Drug Des. 6(6), 569-584; Helene et al. (1992) Ann. N.Y. Acad. Sci., 660, 27-36; and Maher (1992) Bioassays 14(12), 807-815).